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Review article

Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: A global perspective

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ABSTRACT

Neurodevelopmental abnormalities associated with HIV infection have been described since the first reports of pediatric AIDS in the 1980s. Before antiretroviral therapy (ART) became widely available, progressive HIV-1 encephalopathy (PHE) was reported in the US in 13–35% of children with HIV-1 infection and in 35–50% of children with AIDS. Introduction of ART can prevent PHE and reverse PHE present at ART initiation, but a high prevalence of residual problems has been described. Even though 90% of HIV-infected children live in the developing world, few children have access to ART and little is known regarding the neurological manifestations of perinatal HIV infection in those regions.

Mechanisms of pediatric HIV-1 neuropathogenesis and factors associated with neurodevelopmental abnormalities in perinatally infected children are not yet fully understood. Studies have demonstrated that HIV-1 enters the CNS soon after infection and may persist in this compartment over the entire course of HIV-1 infection. The CNS is a distinct viral reservoir, differing from peripheral compartments in target cells and antiretroviral penetration. Neurotropic HIV-1 likely develops distinct genotypic characteristics in response to this unique environment.

We reviewed the literature on pediatric neuroAIDS and identified gaps in the current knowledge.

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1. Pediatric HIV/AIDS epidemic

The HIV/AIDS epidemic continues to grow in most countries and continents. Globally, 40.3 million people were estimated to be living with HIV/AIDS by the end of the year 2005. An estimated 2.3 million children are living with HIV/AIDS, almost 2000 children are infected with HIV each day, and more than 1500 children die each day of HIV/AIDS.[1] Global commitment to rapidly scale up the access to antiretroviral therapy (ART) has led to remarkable progress, although with less success in the provision of ART to HIV-infected children. In the United States and Western Europe, a comprehensive approach to prevention of mother to child transmission of HIV (PMTCT), including ART during pregnancy, elective cesarean section and infant formula feeding, has virtually eliminated pediatric HIV as a public health problem. Even though simple, low-cost PMTCT regimens, such as single-dose Nevirapine, have been developed,[2] PMTCT coverage remains low with less than 10% of pregnant women having access worldwide, resulting in an increasing pediatric HIV epidemic.[3]

2. Neuropathogenesis of HIV-1

Notwithstanding the fact that young children may be more vulnerable to neurological complications of HIV-1 infection, the vast majority of studies into the mechanisms of HIV-1 neuropathogenesis have focused on adults with HIV-associated dementia. It has been well established that HIV-1 invades the CNS early in infection, primarily via infected monocytes/macrophages and CD4+ T lymphocytes.[4–10] Macrophage-tropic forms of HIV-1 preferentially infect the brain,[11,12] and most HIV-1 detected in autopsy brain tissue is found within perivascular macrophages and microglia, the only major cell types in the brain that express both CD4 and chemokine coreceptors necessary for productive HIV-1 infection.[13–18] Products such as viral proteins, proinflammatory cytokines and nitric oxide released from HIV-infected macrophages and microglia lead to a cascade of neurotoxic events. Besides macrophages and microglia, HIV-1 can also infect astrocytes in a CD4-independent, non-productive fashion.[15,17,19–22] Viral interactions with astrocytes may play a more significant role in pediatric HIV encephalopathy as fetal astrocytes may be more susceptible to HIV-1 infection, and because the developing CNS may be more susceptible to perturbations in astrocyte function.[22,23] Productive infection of neurons is still a matter of debate. Recent data indicate that neurons may be actively infected in low abundance in children,[24] but neuronal loss, a major pathologic feature in HIV-associated encephalopathy, is predominantly an indirect consequence of HIV infection.

Neurotropic HIV-1 likely develops distinct genetic characteristics in response to the unique CNS environment, characterized by its specific target cells and suboptimal penetration of several antiretroviral agents.[25,26] This results in the emergence of a compartmentalized viral population. In adults, the compartmentalization of HIV-1 populations in the CNS has been revealed by differences in HIV-1 genetic sequences or drug resistance patterns between blood and CSF,[27–29] postmortem lymphoid or brain tissues.[30–32] Comparable studies in children are limited, although observations of discordant drug resistance mutation patterns in blood and CSF suggest HIV-1 viral populations may be similarly compartmentalized in the CNS of children.[33]

Two properties of HIV-1 CNS infection can reduce the efficacy of antiretroviral treatment at the level of the CNS. First, the ability of antiretroviral drugs to cross the blood–brain barrier is variable, with protease inhibitors in particular having poor CNS penetration.[34–36] This could limit the drugs' effectiveness and may result in the emergence of drug-resistant populations. Second, the relatively long lifespan of macrophages, microglia and astrocytes compared to CD4+ T cells poses a problem for fast elimination of the virus from this compartment as HIV-infected cells can continue to produce virus, viral RNA and potentially neurotoxic viral or cellular proteins over the lifespan of the cell.[37–39] A high extent of compartmentalization in viral load suppression kinetics between plasma and CSF following initiation of HAART has been associated with the presence and severity of symptomatic CNS involvement.[40–42] It is therefore important to better understand the evolution of the child's neurodevelopment following initiation of ART and to document the prevalence of and risk factors for discordance between control of HIV disease in the periphery versus the CNS.[43]

Taken together, studies of HIV encephalopathy in children suggest that the virus and host factors involved in HIV-1 neuropathogenesis and their consequences show many similarities and some important differences to those in adults (Table 1).

3. Pediatric neuroAIDS: experiences in the US and Europe

3.1. *HIV-related CNS disease*

Since the first reports of pediatric AIDS in the 1980s, neurodevelopmental abnormalities have been a well-known

Table 1 – Key features of HIV-1 neuroAIDS in children and adults

Adults	Children
CNS HIV-1 invasion during primary infection, often followed by compartmentalization	CNS HIV-1 invasion during primary infection, likely also often followed by compartmentalization
Target cells include macrophages, microglia and to a lesser degree astrocytes	Same target cells, but astrocytes may play a more central role and neurons may also be actively infected
Long latent period between infection and neurological manifestations	Neurological disease more often the first AIDS-defining illness, even before important immunodeficiency
Deterioration of mature CNS with brain atrophy	Impairment of immature CNS and impaired brain growth
Both motor and cognitive functions deteriorate	Motor, cognitive and language functions are impaired
CNS opportunistic infections and cerebrovascular disease are common	Cerebrovascular disease and CNS opportunistic infections are rare, but the latter may be more frequent in developing countries
Antiretroviral treatment reduces incidence and can reverse neurological manifestations present at start of treatment	Similar preventive and therapeutic effects of antiretroviral treatment on CNS manifestations

complication of HIV disease and cause of significant morbidity and mortality.[44,45] In contrast to adults, where HIV attacks a mature brain and leads to dementia, HIV infection in children impacts on an immature brain and manifests as static or progressive HIV encephalopathy. The symptoms of progressive HIV-1 encephalopathy (PHE) consist of the classic triad of acquired microcephaly, delay or loss of developmental milestones (motor, mental and language) and pyramidal tract motor deficits.[46] Another difference of adult HIV CNS disease from that of HIV CNS involvement in children, especially children under 1 year of age, is that it more frequently occurs before there is significant immunosuppression,[47–49] and is the first AIDS-defining illness in as many as 18% of pediatric patients (Table 1).[50,51]

Before combination ART became widely available, PHE was reported in the US in 13–35% of children with HIV infection and in 35–50% of children diagnosed with AIDS.[47–49,51,52] The highest incidence rate of HIV-related CNS manifestations occurs in first 2 years of life, with incidence rates of 9.9% in the first year of life, 4.2% in the second and less than 1% in the third year of life and thereafter.[47,48,53]

The neuroradiological hallmarks of PHE include cortical atrophy and basal ganglia calcifications on computer tomography scans, and white matter lesions and central atrophy on magnetic resonance imaging.[54] These neuroradiological abnormalities are in general preceded by clinical manifestations and are associated with more advanced disease.[55]

CNS opportunistic infections, CNS lymphoma and cerebrovascular disease do occur but are much less frequent in children compared to adults (Table 1).[56]

3.2. *Neurodevelopmental delays indicative of HIV-related CNS disease*

The reported prevalence of delay in cognition, motor function, speech and language among HIV-infected children has varied from low (8%) to high (>60%), with an increased prevalence with increasing age.[57–71] This disparity in reported prevalence is due to the variability in methodology between studies, differences in study populations, as well as the inherent variability in the severity and timing of neurobehavioral delays in HIV-infected children.

The developmental deficits associated with HIV infection in children include impaired language and motor skills, cognitive deficits, impaired visual–spatial integration ability and impaired executive functions.[53,69,72–75] Delays in motor development, especially gross motor skills, most strongly differentiate HIV-infected from HIV-exposed children,[53,69,76–78] and are seen more frequently in infants than school-aged children.[79] Children demonstrating motor dysfunction, including abnormal muscle tone, less muscle bulk or less muscle strength, have been shown to be at an increased risk for disease progression.[80] Delays in mental development occur later in infancy[53,76,81,82] and most often present as a global cognitive deficit. Differences in specific areas of cognitive function have not been systematically observed in HIV-infected children.[83–85] Delay in language development, especially in expressive language, commonly occurs in young HIV-infected children and often precedes the presence of abnormalities on neurologic examinations or CNS imaging. Language assessment may therefore become a useful tool to determine the best time to initiate therapy or to monitor treatment.[73,74]

Studies on behavioral problems associated with HIV infection have given conflicting results. Some studies found increased behavioral or psychosocial problems in HIV-infected children[71,75,79] while others documented behavioral performance of infected children within normal limits or comparable to HIV-exposed, uninfected children or other control groups.[86,87] Higher rates of behavioral problems may be due to other biological or environmental factors rather than a direct result of HIV infection.[87]

3.3. *Risk factors for pediatric neuroAIDS*

No current measure can predict which children may develop HIV-related CNS disease.[88] Studies on predictors of HIV-associated CNS disease in the US have been hampered by the fact that many HIV-infected children with a diagnosis of developmental delay and/or microcephaly also have a history of premature birth and prenatal exposure to drugs or alcohol, making it difficult to define the cause of their neurological symptoms.[89]

Factors that have been associated with high prevalence rates and more severe CNS disease include maternal and

child immune status, elevated CSF and plasma viral load, timing of infection, route of transmission and treatment availability. The risk of encephalopathy is higher among HIV-infected children born to mothers with more advanced disease as measured by CD4+ cell count and viral load at the time of delivery.[90] Children with more advanced degrees of immune suppression early in life and those with high-plasma viral load in infancy also have higher rates of encephalopathy.[48,49,63,67,81,90–92] High-CSF viral load has been associated with neurocognitive impairment in some studies.[93,94] Vertically infected children, who represent over 90% of pediatric HIV infections, are more likely to experience CNS disease, and children with intra-uterine infection are more likely than those with peri- or post-partum vertical infection to develop early onset, rapidly progressive and severe PHE.[67,68] Environmental factors that pose a risk to a child' s development, such as maternal drug and or alcohol use, poverty, low maternal education and poor quality of the home environment have also been demonstrated to be associated with neurodevelopmental delay.[95–97]

3.4. *CNS disorders as predictors of HIV/AIDS disease progression*

Neurobehavioral assessments can provide predictive information beyond that obtainable from biological markers of HIV disease status such as CD4 count and HIV RNA level.[80] Children in whom signs of encephalopathy appear in the first year of life have greater severity and shorter survival than those in whom encephalopathy appears later, and low cognitive and motor scores at 4 months of age have been shown to be significant predictors of early mortality.[59,98] The presence of HIV-related CNS disorder also causes significant impairment of the child's overall functioning, lowers the quality of life and is associated with increased hospitalizations.[48,53,99] Many HIV-infected children have reduced performance at school, which can lead to school drop-out, perpetuating the cycle of poverty unless they have access to special services.[75,100]

3.5. *The effects of HAART on HIV-1 CNS manifestations*

Treatment with a combination of antiretroviral drugs results in a decline in plasma and CSF viral load,[33] can reverse CNS manifestations,[33,101–106] and reduces the risk and severity of HIV encephalopathy.[85,107–111] With widespread access to ART, the rate of PHE in the US has decreased from 21–35% to less than 2%.[89] Similarly, experience in Spain indicates a decrease in PHE incidence from 9.3% in the early years to 0–1.5% in the HAART era.[108] Unfortunately, ART does not eliminate HIV-related CNS manifestations. While reversible cognitive impairment has been documented in 30% of cognitively impaired adults, it persisted in 70% of cases, despite a mean duration of 3 years ART, and the baseline level of cognitive impairment was strongly associated with the reversibility of the impairment.[105,112] Experience with children on ART revealed a high rate of arrested HIV-related encephalopathy but also high rates of residual behavioral problems, neurologic, cognitive and scholastic impairments, and risk for relapse of PHE.[71,89] The risk of CNS disease in children being treated with HAART may be higher among children with moderate CT brain scan abnormalities and children with CD4+ cell counts below 500. The cognitive effects in these children may be a result of ongoing viral replication in the CNS despite virological control in the periphery, or residual effects of static HIV-related CNS disease.[113]

4. Pediatric NeuroAIDS: experiences in developing countries

It is highly unlikely that the data from the US and Europe are directly applicable to other parts of the world, because of differences in substance abuse in HIV-infected pregnant women, in prevalence of malnutrition and opportunistic infections, and in child-rearing environment.[114] It is therefore surprising that, even though more than 90% of HIV-infected children live in the developing world, few studies have investigated the neurological manifestations of HIV-infected children outside of the US and Europe.

A small study in Rwanda, using a simple screening tool to primarily detect severe delay, demonstrated that 15–40% of HIV-infected children showed delay in their development, predominantly in gross motor developmental skills.[115] After excluding children with AIDS, the proportion of HIV-infected children with abnormal neurodevelopment was 12.5% at 6 months, 16% at 12 months, 20% at 18 months and 9% at 24 months of age, compared to 5% or less for any age group of HIV-exposed uninfected children.

Impaired global cognitive performance was demonstrated in asymptomatic HIV-infected children in the Democratic Republic of Congo (formerly Zaire) in both HIV-infected and HIV-exposed, uninfected children, suggesting that the characteristics of the home environment and the impaired health of the mother may affect development.[116]

Ugandan HIV-infected infants demonstrated a high probability of abnormal neurologic examination by 12 months, scored lower on both mental and motor development, and demonstrated greater deceleration in their rate of motor development compared to HIV-exposed uninfected infants and a control group. At age 12 months, 30% and 26% of HIV-infected infants had delay in motor and cognitive development, respectively, compared with 11% and 6% among HIV-exposed, uninfected children and 5% and 6% among HIV-unexposed infants.[72] Assessments of these children at age 6–12 years showed no significant differences in neurologic, motor and psychometric development compared to age- and gender-matched seroreverters and HIV-negative children. In the absence of HAART, these children likely represented a subgroup of HIV-infected child survivors with less aggressive disease, whereas children with progressive encephalopathy may not have survived to the school age.[117]

A study of Tanzanian children born to HIV-infected mothers demonstrated that both infected and exposed children had slower mental and motor development over time than would be expected for their age, with impaired motor function appearing before impaired mental function. Testing HIV-1 positive in the first 21 days was associated with a 14.9

(95% CI 5.0, 44.7) and 8.7 (95% CI 3.0, 25.1) times higher rate of becoming developmentally delayed in terms of mental and motor function, respectively, when compared with HIV-uninfected children. Testing positive after the first 21 days of life was associated with a 3-fold increase in the rate of both mental and motor delay. The Bayley scores for all children decreased with increasing age, likely reflecting a cumulative risk of poor neurodevelopment caused by poverty and HIV morbidity, as well as the multiple demands placed on families caring for HIV-infected members and periods of separation between mother and child.[118]

Unfortunately, no data are available on the effect of HAART on pediatric neuroAIDS in sub-Saharan Africa.

Several publications have described the experiences in Latin America. In Brazil, there is a high prevalence of mild neurological abnormalities in both HIV-infected and HIV-exposed children.[119,120] Significantly lower developmental quotients were observed among HIV-infected but not HIV-exposed, uninfected children.[120] A hospital-based study of 340 HIV-positive children in Brazil (1985–1998) found a 32.5% prevalence of encephalopathy, a 49% prevalence of neurological manifestations and many children with educational and behavioral difficulties.[121,122] A relatively high number of children (34%) developed CNS opportunistic infections, 11% of which were due to bacterial infections, 22% to opportunistic infections (cytomegalovirus, toxoplasma, cryptococcus and *Mycobacterium tuberculosis*), and 1.3% to syphilis. Cerebrovascular disease was noted in 2.5% of children.

Among 784 HIV-infected Argentinean children, 311 developed CNS disease, predominantly (92%) encephalopathy.[55] CNS manifestations were the presenting symptom in 29% of children. The prevalence of opportunistic CNS infections and cerebrovascular disease was low (<1.5%). ART resulted in improvement of the neurodevelopment and reversion of acquired microcephaly.

Experiences from Asia are exceptionally scarce.[123,124]

5. Challenge of defining the CNS burden attributable to HIV infection in children

The determination of whether a child's neurobehavioral deficit is related to HIV disease as opposed to other medical, environmental or social factors is critical.[88,125,126] Low levels of maternal literacy, poor socio-economic status, poor quality of interaction between caregivers and child, low birth weight and anemia may all be more frequent in HIV-infected children. In developing countries, zinc deficiency, protein malnutrition and childhood encephalopathies such as cerebral malaria and bacterial meningitis, may also be more frequent among HIV-infected children. Monitoring these variables over time poses a major challenge to determining the incidence of HIV-attributable CNS disease in children. In addition to potential confounders and effect modifiers at the individual level, other factors such as maternal HIV disease and the hardship thereof imposed upon the family, may influence maternal interaction and bonding received by the child. Disentangling the effect of HIV infection in the mother from the direct effect of HIV infection in the child adds another level of complexity to the study of pediatric neuroAIDS.

Limited work has been performed to validate the standard neurobehavioral assessment tools in regions outside the US and Europe. Investigators have based their assessments on parental reporting of selected items,[127] simple screening tools,[115] or cultural adaptations of standard measurement tools.[72,126] While the assessment of motor, mental, language and behavioral development may need to vary across ages, sex, cultural and linguistic groups, the wide variability in the methodology applied reduces the external validity of results. To increase the comparability of results between populations, one could promote the use of the recently published HIV encephalopathy classification system based on the Bayley Scales of Infant Development II.[88]

6. Conclusion

Whereas the pediatric HIV/AIDS epidemic in the US and Europe is virtually eliminated, the problem in other regions of the world, especially sub-Saharan Africa, is still growing. Neurodevelopmental delay is clearly associated with HIV infection, and exposure to the virus in utero may also have an impact on children's development. Access to PMTCT for all pregnant women and universal access to ART for all eligible children is thus urgently needed.

PHE is the most common CNS disorder among HIV-infected children worldwide. While PHE is an ART eligibility criterion,[128] neurobehavioral assessment is rarely performed in developing countries due to a shortage of skilled human resources and lack of validated assessment tools for these settings, resulting in missed opportunities for timely initiation of ART and other strategies for prevention and care of HIV-associated neurodevelopmental impairment. Validation and standardization of neurodevelopmental assessment tools for developing-world contexts will be key to our ability to identify early warning signs of HIV-associated CNS disorders, and to allow the integration of neurodevelopmental assessment into pediatric HIV care and treatment programs worldwide.

Providing ART to HIV-infected children in resource-poor countries will however demand a holistic approach that goes beyond the "simple" administration of antiretroviral drugs, as ARVs can improve quality of life and lengthen survival, but may not eliminate the virus from the CNS. Optimal prevention and treatment of pediatric neuroAIDS will also demand enhanced knowledge on optimal timing of ART initiation and the identification of ART regimens with the highest efficiency in eliminating HIV from both the peripheral and the CNS compartment.

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